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INTRODUCTION:

The purpose of this Phase 2 clinical trial is to determine if an oral, orange flavored suspension of D-methionine can prevent noise-induced hearing loss (NIHL) and tinnitus in our troops.

Hypotheses:

Primary Hypothesis: Administration of oral D-methionine prior to and during weapons training will reduce or prevent permanent NIHL.

Secondary Hypothesis: Administration of oral D-methionine prior to and during weapons training will reduce or prevent noise-induced tinnitus.

Primary outcome to test the primary hypothesis: Pure tone air-conduction thresholds.

Primary outcome to test the secondary hypothesis: Tinnitus questionnaires.

Specific Aims:

1. To determine whether administering oral D-methionine (D-met) can prevent permanent NIHL after weapons training. This aim will be addressed by comparing the results of D-met versus placebo administration starting 3 days prior to, during the 11 day period of weapons training (Monday-Friday of week 1 and Monday-Thursday of week 2), and 4 days after for a total of 18 days. Pure tone hearing thresholds will be assessed before and 19-22 days after completion of weapons training (i.e., 15-18 days after the last day of study drug/placebo administration).
2. To determine whether administering oral D-met can prevent tinnitus after weapons training. This aim will be addressed by comparing the results of D-met versus placebo administration starting 3 days prior to, during the 11 day period of weapons training (Monday-Friday of week 1 and Monday-Thursday of week 2) and 4 days after for a total of 18 days. Tinnitus questionnaires will be assessed before and 19-22 days after completion of weapons training (i.e., 15-18 days after the last day of study drug/placebo administration).
3. To monitor for any potential side effects of D-met in human subjects. This aim will be accomplished by subject query on each day of drug administration with routing of any adverse event reports to study medical personnel, statisticians and to the Food and Drug Administration (FDA).

Primary Endpoints

- 1) Primary endpoint is to confirm safety and tolerability of up to 100 mg/kg daily given in divided doses 12 hours apart.
- 2) Primary efficacy endpoint is change from baseline in pure-tone threshold as measured by absolute change and frequency of significant noise-induced threshold shift (STS).
- 3) Secondary efficacy endpoint is change from baseline scores for the tinnitus scales for both loudness and annoyance.

Study Design:

This prospective study is a randomized, double-blind, placebo-controlled Phase 2 clinical trial of oral D-met to reduce NIHL and tinnitus. The goal of the study is to develop a safe oral pharmacologic agent to augment physical hearing protectors for noise exposures that exceed the protective capabilities of ear plugs and/or muffs. The study population is a cohort of Drill Sergeant (DS) instructor trainees during and 21 days after their 11 days of weapons training. The primary objective of this study is to determine the efficacy of D-Met in preventing or reducing NIHL and tinnitus secondary to a minimum of 500 rounds of M-16 weapons training occurring over a 2 week period. A total of 600 Drill Sergeant Instructor Trainees will be enrolled in the study and randomized to study drug or placebo for a final study cohort of 504 subjects. Subjects will be recruited during the first week of training. Participation will consist of an on-site Screening visit followed by a Baseline visit (Study Visit 1), and an End of Study visit (Study Visit 3), for a total of 3 Study Visits for each subject. Compliance and adverse event checks will be performed daily throughout the drug administration period. Subjects will be prescreened to review inclusion/exclusion criteria and medical history. Baseline and final audiologic testing will include otoscopy, tympanometry, and pure-tone hearing threshold testing at .5, 1, 2, 3, 4, 6, 8 kHz bilaterally. Tinnitus will be measured using standardized tinnitus assessment questionnaires. Subjects will take either the oral study drug or flavor matched placebo twice per day for 18 days starting 3 days prior to the weapons training, during the weapons training period and for an additional 4 days. Data will be independently analyzed through the Yale Occupational and Environmental Medicine Program. Data will be analyzed to determine 1) if there is a significantly reduced change in hearing threshold in the average of both ears for the D-met group as compared to the placebo group at the tested audiometric frequencies, 2) to determine if there is a significantly lower rate of significant threshold shift (STS) according to the Defense Occupational Environmental Health Readiness System- Hearing Conservation (DOEHRSHC) in either ear for the D-met group as compared to the placebo group 3) to determine if there is a significant difference in reported level of tinnitus between the D-met and the placebo groups and 4) to detect, report and analyze any side effects. This study is a collaboration among Southern Illinois University School of Medicine, the U.S. Army, and Yale University. The study includes a regulatory consultant to ensure full compliance with all regulatory agencies, committees, and boards. It is hoped that this study will move us forward in preventing NIHL and tinnitus world-wide.

Relevance: This study will test the hypotheses that oral D-met can prevent or significantly reduce permanent NIHL and potentially tinnitus in US military troops during weapons training in a cohort of experienced soldiers.

BODY:

The original Statement of Work (SOW) outlined several tasks to be completed within the first year of the grant before data collection could begin. We have completed or nearly completed all appropriate documents for submission to the appropriate regulatory agencies for approval. In addition, the study drugs have been formulated, undergone

stability testing and are ready for shipment to the testing site. Once all regulatory approvals are granted, all personnel are in place and the Manual of Operations is completed and approved, we will initiate recruitment and begin data collection. Below are our original SOW tasks planned for the first year of the granting period (March 1, 2011 to March 31, 2012) and the accomplishments made on each task to date:

SOW Task 1: *To submit a complete Investigational New Drug (IND) Application to the FDA:* We have made substantial progress in preparing our IND application for the FDA and we anticipate submission to the FDA by the end of May 2012. We anticipate the IND application to include at least 8 to 9 volumes (280-300 pages per volume).

We are awaiting a signed FDA Form 1572 from CPT Callis, the Principal Investigator on-site in order to make our final IND submission. CPT Callis has proposed some last minute changes in the clinical protocol which will be completed by the first week of April, 2012. We were also notified by LTC Sonja Cable on March 23, 2012 that although the protocol was approved by the previous Deputy Commanding General-Initial Military Training (DCG-IMT), due to changes in leadership, the clinical protocol now requires vetting by the current (DCG-IMT), Training and Doctrine Command (TRADOC) Surgeon, Drill Sergeant School Commandant and Deputy Commandant. We anticipate these approvals to be completed by the end of May 2012. At that time, we will submit all documents to the FDA.

SOW Task 2: *To submit a completed Institutional Review Board (IRB) application:* We originally submitted the protocol to the Southern Illinois School of Medicine (SIUSOM) IRB for review in April 2011. Subsequently, we were advised by the DoD Human Subjects Protection Scientist, Julie Wilberding, PhD, and the Human Research Protections and Compliance Administrator, Ms. Michelle Christiano, BBA, CCRC, CIP, to consider relying on the Fort Jackson local IRB as the IRB of record for this study instead of the SIUSOM IRB. The Dwight D. Eisenhower Army Medical Center (DDEAMC) IRB has regional jurisdiction over the local investigative site (Moncrief Army Medical Center) therefore the IRB of record will be the regional oversight or DDEAMC. An IRB Authorization Agreements (IAA) will be executed by the end of April 2012.

All DDEAMC IRB documents are near completion but require the input from CPT Callis (Principal Investigator on-site) before finalization. When CPT Callis gives his final approval of the documents and after we are assigned an IND number from the FDA, CPT Callis will electronically submit completed documents to the DDEAMC IRB for their approval.

SOW Task 3: *To complete the Hiring of Study Staff and finalize corporate contracts*

- a. Yale Occupational Environmental Medicine Program: The Subcontract for Yale has been finalized and is in force. Dr. Campbell met with the Yale team in person on March 12, 2012.

- b. Ft Jackson: We were notified on March 2, 2012 by Dr. Dwayne Taliaferro of a procurement advisory notice (PAN) in which we would not be allowed to transfer funds to Ft Jackson. This was unanticipated despite our attempts to obtain clarification regarding the necessary agreements to conduct this study at Ft Jackson. We are exploring options for hiring personnel through SIU to work at the Ft Jackson site. We can purchase the equipment through SIU and ship it to Ft Jackson for the study. Unfortunately, that means that Ft Jackson will not be able to retain the equipment at the end of the study as originally planned.
- c. SIUSOM: All study personnel for the SIUSOM site have been recruited/trained and are currently working on different phases of the project.

SIU Center for Clinical Research: In the initial grant budget was allocated for software for the Clinical Trials office. At the time the grant was written, the Clinical Trials office was newly formed and we were uncertain of the role they would play in this project. However, they have been enormously helpful in preparing the IRB and FDA documents and in fact hired another full time staff person, Jill Anderson PhD specifically for this project. Therefore, when we discovered that we will not be able to execute a CRADA to transfer funds to Ft. Jackson for personnel, it was proposed that for the first year of this grant, the personnel funds be allocated to the Clinical Trials center to cover their staff time on this project and then in subsequent years, the personnel money will be used for personnel at the Ft. Jackson site as soon as we finalize the logistics of hiring personnel for the Ft. Jackson site through SIUSOM and not with t transfer of funds to Ft. Jackson.

- d. KP Pharmaceuticals: The Active Pharmacological Ingredient (API) was obtained in August 2011. KP Pharmaceuticals completed all validation tests in early January 2012. The study drug and placebo formulations, including the 30 day stability test reports, were completed in early March 2012. KP Pharmaceuticals has sent all the final information to the FDA consultant for incorporation into the IND documents. The study drug and placebo are ready and available for shipping to the study site.
- e. Judi Weissinger, PhD: The contract for Dr. Weissinger is finalized and in force. Dr. Campbell flew out and met with her in August, 2012 to facilitate interactions for the FDA IND filing. Dr. Weissinger had surgery in November with some complications which have not fully resolved. However, she still plans to finalize our documents for IND submission by the end of April.
- f. Colleen Le Prell, PhD: Dr. Le Prell's consulting contract is being handled as a PO through the University of Florida at their request. However, our clinical trials office at SIUSOM is much better established now than it was at the time of grant application. Subsequently, we are doing much more of the work here that was initially budgeted for Dr. Le Prell. It has been much easier and faster to coordinate much of this preparatory work using our own clinical research core.

We wish to retain Dr. Le Prell for assistance as needed, however we would like to rebudget some of her funding to support the clinical trials office at SIUSOM to complete much of the work initially delegated to Dr. Le Prell. We have hired a Post Doc audiologist, Jill Anderson AuD, PhD in our clinical trials office to focus just on this project. She started work November 28, 2011 and is already providing valuable assistance to this project.

SOW Task 4: *To complete study Site Visits*

- a. Dr. Campbell has traveled to the study site on two occasions to finalize the study protocol/logistics and met with site leadership/study personnel. The initial visit was made on December 11-13, 2008. Due to significant changes in personnel at Ft Jackson, a subsequent site visit was made on October 3-5, 2011 to orient new personnel to the study protocol.
- b. An on-site visit and audit of KP Pharmaceuticals will be performed prior to study onset. However, the date of the audit has not yet been scheduled.
- c. The on-site visit of the entire study team has not yet occurred. However, the local study team has been meeting weekly throughout the planning and preparatory period. Weekly conference calls since January 2012 have included Ft Jackson personnel, specifically CPT Callis. Dr. Campbell has also conducted a conference call with 1LT Best-Bailey and CPT Ludwig, the 2 audiologists at Ft. Jackson on April 3, 2012 to review all study procedures and answer questions.

SOW Task 5: *To complete all necessary study documents.*

All study documents are completed except for the clinical protocol which is being revised per CPT Callis' request. These documents will be submitted for final review by Ft Jackson the first week of April. The Manual of Operations is in draft form awaiting final approval by Ft Jackson.

SOW Task 6: *To recruit subjects for first pilot data.*

Subjects have not yet been recruited. Commencement of the study is contingent upon regulatory approvals.

SOW Task 7: *Send pilot data to Yale for data checking*

Commencement of the study has not yet occurred. Pilot data has not been collected.

SOW Task 8: *To continue enrollment and recruitment with new classes starting every 2-3 weeks*

Subject enrollment has not yet begun.

KEY RESEARCH ACCOMPLISHMENTS:

- Corporate contracts are in place
- All SIUSOM clinical trial personnel are hired, trained and completing assignments
- Study drug and placebo have been formulated, tested and are ready for shipment
- All sections of IND have been drafted
- All Military IRB documents have been drafted
- Initial on-site visits have been made

REPORTABLE OUTCOMES:

To date, there are no reportable outcomes as the clinical trial has not yet begun.

CONCLUSION:

Excellent progress has been made regarding the start-up issues during the first 12 months of the grant. However, we were frustrated by the many delays that occurred along the way:

Delays in the Drug Formulation

- 1) First Quarter (March 1, 2011 through May 31, 2011): Before the contract to KP Pharmaceutical could be issued, Dr. Campbell had to provide a justification for sole source provider to the State of Illinois and have it approved. KP Pharmaceuticals also had to apply to the Illinois Department of Human protections to ensure that they did not discriminate in any hiring practices. These filings also generated additional costs. . After that approval was finalized, the contract was constructed through the grants and legal offices of SIUSOM. The contract for KP Pharmaceuticals for drug and placebo formulation was sent to them. However once the contract was in place, KP Pharmaceuticals found that the former API drug supplier no longer produced D-methionine. Although they had been notified in November of 2010 that the grant would be funded, they waited until they actually had a signed contract before ordering the API drug source. The cumulative total time for these delays was 9 months. However all of these delays have been overcome and the drug and placebo supplies are now ready for use.
- 2) Second Quarter (June 1, 2011 through August 31, 2011): As detailed from the first quarter, we were delayed on our IND filing with the FDA because KP Pharmaceuticals could no longer obtain the GMP grade source API D-methionine from our previous supplier. Because KP Pharmaceuticals thought they could obtain GMP from the previous supplier, they did not explore other options earlier. KP Pharmaceuticals did not find a new supplier until late August. Although we had adequate testing for our previous batches of raw D-met for prior clinical trials to prevent cisplatin-induced hearing loss and radiation-induced oral mucositis, the use of a new supplier for the raw API D-met required new testing. KP Pharmaceuticals had initially anticipated drug formulations to be completed by the end of July with shipments to the clinical trials site

ready by mid-August. However with the new supplier issue, the formulation was significantly delayed.

- 3) Third Quarter (September 1, 2011 through December 15, 2011): The API drug was finally obtained in August but the 30 day stability tests were not yet finalized during this period.
- 4) Fourth Quarter (December 15, 2011 through March 1, 2012): KP Pharmaceuticals did not complete all validation tests until early January 2012. The study drug and placebo formulations, including the 30 day stability test reports, were not completed until early March 2012. KP Pharmaceuticals sent all the final information to the FDA consultant for incorporation into the IND documents. The study drug and placebo are now ready and available for shipping to the study site.

Delays with the FDA Consultant

- 1) First Quarter (March 1, 2011 through May 31, 2011): The contract for Dr. Weissinger, our FDA regulatory consultant was delayed by several months because she did not have the 5 million dollar professional liability insurance usually required by SIUSOM. On June 6, 2011, we received a waiver from our legal office for that requirement. Fortunately, Dr. Weissinger was willing to work with us on the FDA filing prior to her contract being finalized so that we were not delayed in moving forward.
- 2) Second Quarter (June 1, 2011 through August 31, 2011) Dr. Campbell flew out and met with her in August 2011 to facilitate interactions.
- 3) Third Quarter (September 1, 2011 through December 15, 2011) Dr. Weissinger had to unexpectedly undergo trigeminal neuralgia surgery in November with major complications which have not fully resolved. Although Dr. Weissinger planned to finalize our documents for IND submission by early January, she was not physically able to work at the pace she anticipated but is proceeding now.
- 4) Fourth Quarter (December 15, 2011 through March 1, 2012): We finished all sections of the IND document and sent them to our FDA consultant on December 20, 2011. However, we have experienced additional delays due to suggested modifications in the toxicology and pharmaceutical reporting sections of the IND by Dr. Weissinger. We are now working with her to finalize these documents and submit them prior to the end of May, 2012 when we should receive final approval from the military on the changes that they want to implement in the clinical protocol section of the IND.

Delays at Fort Jackson

- 1) First Quarter (March 1, 2011 through May 31, 2011): We tried to process our contract with Ft. Jackson but the new administrator had difficulty finding the forms and procedures for the required CRADA. Initially it had been drawn up as a standard university subcontract.
- 2) Second Quarter (June 1, 2011 through August 31, 2011) We received the CRADA template forms from Christopher Baker, our contract officer from the US Army, but did not receive instructions on how to appropriately implement the agreement. In addition,

the Drill Sergeant Instructor training school modified the schedule for weapons training which required us to change our forms and filing materials.

- 3) Third Quarter (September 1, 2011 through December 15, 2011): Our legal office pointed out that the CRADA forms sent to us were tailored more for the DoD to contract services from us rather than us contracting with Ft. Jackson. The CRADA form stated that we could not proceed with the CRADA until we had obtained approval for our study from the military IRB. We were not familiar with the processes for hiring study personnel at Ft. Jackson and asked Major Mathis to help us identify the human resource personnel who will be assisting us with these new hires. We have not yet obtained that source. However Dr. Campbell did fly to Ft. Jackson October 3-5, 2011 and met with Major Mathis, 1Lt Best-Bailey, Col Page, Mr. Cruz, the instructors for the Drill Sergeant Instructor Training School and others to discuss all procedures for the grant including planned hiring of personnel. We had obtained Ft. Jackson forms for hiring personnel and had filled them out to facilitate future hiring at Ft. Jackson.
- 4) Fourth Quarter (December 15, 2011 through March 1, 2012): We were just informed by Mr. Christopher Baker and Dr. Dwayne Taliaferro on March 2, 2012 that we will not be able to use a CRADA to transfer funds to Ft. Jackson. Therefore, we are now working to determine which options are available to us for hiring personnel to assist at the Ft. Jackson site and to purchase the needed equipment. The equipment purchase should not be overly problematic except that SIU will then retain ownership which was not in our original plan. Hiring personnel through SIU to work at Ft. Jackson could be problematic but we are exploring all options and feel confident that we can resolve these issues. We have focused on preparation and submission of all required regulatory documents and Internal Review Board (IRB) applications and submissions.

Delays due to changes in Personnel

- 1) First Quarter (March 1, 2011 through May 31, 2011): Throughout the planning and submission process for the grant, the primary coordinator at the Ft. Jackson site was Major Curry-Mathis. We did coordinate approvals prior to submission with the other key players at Ft. Jackson but Major Mathis was always our primary point of contact. However, once the grant initiated we found that she would be deployed elsewhere later in the year.
- 2) Second Quarter (June 1, 2011 through August 31, 2011)
- 3) Third Quarter (September 1, 2011 through December 15, 2011): During this quarter Major Mathis was redeployed as described above. On October 3-5, 2011 Dr. Campbell flew down to Ft. Jackson and met with all key players to facilitate the change in personnel. However, at that time, it was determined that the PI needed to be an MD for a FDA IND submission. The conclusion from the meeting with Col Page, Major Curry Mathis and Dr. Campbell was that Col Page would appoint CPT Callis to the position. However, CPT Callis was on foreign deployment at the time.
- 4) Fourth Quarter (December 15, 2011 through March 1, 2012): Communication with CPT Callis did not begin until the first of January 2012 because he did not arrive to Ft. Jackson until December 2011 and then immediately took personal leave. Although the clinical protocol was sent to him in January 2012, CPT Callis did not express concerns or submit his comments on the clinical protocol until March 23,

2012. CPT Callis prefers not to sign the FDA Form 1572 until all his protocol suggestions have been addressed. In addition, after his suggestions have been incorporated into the protocol it will have to be vetted up the ranks of his superiors.

Overall, all contracts are signed and in force other than the CRADA with Ft. Jackson.

In addition, KP Pharmaceuticals has obtained the active pharmacological ingredient (API) for the study drug and has completed formulations of both the study drug and the placebo. The 30 day test samples are ready for FDA submissions but they are finalizing all paperwork for the FDA submission with our consultant. We are also working with the DoD to get the CRADA in place and to obtain a replacement for Captain Callis at Ft. Jackson when he deploys to another site.

Immediate Future Plans:

- We recently discovered (March 2, 2012) that we will not be able to transfer funds to Ft. Jackson. Therefore we are exploring other options for hiring personnel to conduct the study at Ft. Jackson without transferring funds. We will work on purchasing the equipment through SIU.
- We will obtain a signed FDA Form 1572 from CPT Callis upon his approval of the changes in the clinical protocol.
- We will file our IND with the FDA. Sometimes the FDA requests a meeting directly at the FDA and if so we will travel to the FDA to accommodate that request.
- After filing our IND application and receiving an assigned IND number, we will submit application to the Military and Yale University IRBs.
- KP Pharmaceuticals has completed formulation of all drug and placebo supplies for the clinical trial. They will finalize all the paperwork with our FDA consultant to be included in our IND submission.
- We will finalize our Manual of Operations. It is largely finalized now pending final copy of our IND from the FDA consultant.
- We will finalize our PowerPoint presentation that describes the clinical trial for potential subjects and route it through the appropriate channels at Ft. Jackson. We have a draft of the presentation but will need to edit it before presentation to reflect any changes.
- We will start processing hiring procedures for study personnel at the Ft. Jackson site and initiate hiring as soon as we resolve the new funding issue.
- As soon as FDA IND approval is obtained, we will travel to the Ft. Jackson site for a study team meeting to finalize and clarify all procedures. We will then initiate the pilot data collection section of the study.
- Our FDA consultant believes the FDA may request some dietary monitoring for the soldiers involved in this study. We have now obtained all the menus for all meals served to our test population in case we need it. The only possible risk would be if a soldier was extremely protein deprived which appears highly unlikely. However we

have decided to exclude vegetarians from the study. This should have little if any impact on subject recruitment.

- As specified above, we had experienced some delays in processing contracts; however all of the contracts are now in place with the exception of the problems we were informed of March 2, 2012 in that we cannot transfer funds to Ft. Jackson.
- We have obtained the forms and procedures for hiring personnel at Ft. Jackson and are preparing them to start obtaining approvals in advance. However the approvals could take time. Now this process is on hold until we can resolve how to hire personnel without transferring funds to Ft. Jackson.
- We previously had a problem with drug formulation but those problems are solved and the formulations are completed.

Overall, we are very appreciative of the number of individuals in the US Army in research administration and at Ft. Jackson, Yale, the University of Florida, KP Pharmaceuticals, SIUSOM legal (counsel), clinical trials and grants offices, and our consultants that have been willing to patiently work with us on performing the extra work required for this collaboration to successfully move forward. We are all fully committed to preventing noise-induced hearing loss and tinnitus in our troops. We are very grateful for this opportunity.

REFERENCES: N/A

APPENDICES: N/A